the composition of claim 57.--

--73. (New) The method of claim 72, wherein the cancer is of epithelial origin.--

--74. (New) The method of claim 72, wherein the cancer is of neuroectodermal origin.--

--75. (New) The method of claim 74, wherein the cancer of neuroectodermal origin is a melanoma.--

--76. (New) The method of claim 72, wherein the administering is effected at two or more sites.--

--77. (New) The method of claim 76, wherein the administering is effected at three sites.--

REMARKS

Claims 44 and 46-56 are pending in the subject application. By this Amendment, applicants have canceled claims 44 and 46-56 without prejudice without prejudice to the applicants' right to pursue the subject matter of these canceled claims in a continuation or divisional application. Applicants have added new claims 57-77. Support for new claim 57 may be found inter alia on page 11, lines 13-20, page 54, lines 12-14, page 65, lines 12-15, page 85, lines 9-14. Support for new claims 58-70 may be found inter alia from pages 11 to 14. Support for new claim 71 may be found inter alia on page 43, lines 4-9. Support for claims 72-77 may be found inter alia on page 15, beginning line 27 to page 18, line 9. Accordingly there is no issue of new matter and applicants respectfully request the entry of this Amendment. Upon entry, claims 57-77 are under examination.

Figure 6

Applicants acknowledge the Examiner's rejection and will provide a new Figure 6, labeling the y-axis as IgG antibodies upon the indication of the allowance of this subject application.

Double Patenting

The Examiner provisionally rejected claims 44, 46-56 under judicially created doctrine of obviousness-type double patenting as being unpatentable over claimed invention of co-pending Application Nos. 08/481,809, 08/477,097 and 08/475,784. The Examiner suggest applicants provide terminal disclaimers to obviate the obvious type double patenting rejection over the claimed invention of the co-pending applications.

In response but without conceding the correctness of the Examiner's position and to expedite the prosecution of this application, applicants have hereinabove canceled claims 44 and 46-56 without prejudice and added new claims 57-77 in this subject application. For the pending applications, U.S. Serial Nos. 08/481,809, 08/477,097 and 08/475,784, applicants have added new claims to obviate the raised double patenting rejection. For the Examiner's information, applicants have another pending application U.S. Serial Nos. 08/196,154 which has the same specification as this subject application, in which applicants have added new claims. Applicants believe that when the claims of these five applications are compared, there is no issue of double patenting. Accordingly, applicants respectfully request the reconsideration and withdrawal of the above ground of rejection.

§112, First Paragraph Rejection

The Examiner rejected claims 44, and 46-56 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most

nearly connected, to make and/or use the invention for the reasons set forth in the Office Action mailed 6/10/96.

The Examiner stated that applicants essentially argue the reference by Fung, et al. should not be used to question whether antibodies against the ganglioside conjugate vaccines will prevent cancer, since the experiments as set forth by Fung, et al. were not used to study whether GM2-KLH conjugated vaccine prolonged survivability. The Examiner stated that applicants further argue there is no evidence by Fung, et al. that the cancer express GM2, nor the antibodies to GM2 were generated after vaccination. The Examiner stated that applicants arguments are not persuasive to obviate the rejection. Whether or not the objective of Fung, et al. experiments was to determine the efficacy of the GM2-KLH conjugated vaccine is not sufficient to overcome the rejections. As set forth previously, the Examiner stated that since the production of high titers of antibodies in melanoma patients with the GM2-KLH does not appear to correlate with the prevention of cancer as exemplified by the teachings of Fung, et al., it is unpredictable if the composition as claimed is efficacious as a vaccine. Beyond this, the Examiner stated that applicants arguments are not sufficient to obviate the rejection since the art as exemplified by Cohen, et al. (see Science 262:851-843 especially page 843) states: "Cancer vaccines are highly experimental." The Examiner stated that since the specification provides insufficient guidance of how to use the composition as a vaccine and the art at the time of the invention set forth cancer vaccines are highly experimental, it is reasonable to conclude a skilled artisan would be forced into undue experimentation to practice the claimed invention.

The Examiner stated that the specification provides insufficient guidance of how to use derivatives of KLH as recited. The Examiner stated that applicants assert that by routine experimentation, one skilled in the art is enabled to make

derivatives of KLH. The Examiner stated that applicants' arguments are not persuasive.

The Examiner stated that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess, et al.). The Examiner stated that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar, et al.). The Examiner stated that Rudinger, et al. teaches "particular amino acids and sequences for different aspects of biological activity can not be predicted a priori, but must be determined from case to case by painstakingly experimental study" (see page 6). The Examiner stated that Salgaller, et al. teaches modifications (i.e. deletions) of the amino acid structure of peptide can alter the activity of the protein. The Examiner stated that Fox, et al. teaches methods for determining fragments which have antigenic activity is unpredictable. The Examiner stated that these references demonstrate that an even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity of a protein. The Examiner stated that in view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad or derivatives and fragments encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

The Examiner has withdrawn the rejection of the objection to the specification for not providing sufficient guidance on the

synthesis of conjugates with other ganglioside or chemically modified ganglioside.

In response, applicants respectfully traverse the above ground of rejection. Applicants have hereinabove canceled claims 44 and 46-56 without prejudice. New claims are directed to a composition comprising a ganglioside conjugated through the ceramide portion of the ganglioside to a Keyhole Limpet Hemocyanin or a derivative thereof and an adjuvant, the amounts of such conjugated ganglioside and such adjuvant being effective to stimulate or enhance antibody production in a subject, and a pharmaceutically acceptable carrier and uses of said composition. Accordingly, new claims are not directed to vaccine and thereby render the rejection to the vaccine claims moot.

Regarding the Examiner's statements about the derivatives of Keyhole Limpet Hemocyanin, applicants maintain that the specification have provided enabling teachings to generate such derivatives. See Specification page 12, lines 4-13. Applicants have also described some routine experiments on page 4, second paragraph of the January 6, 1997 Supplemental Communication in Response to June 10, 1996 Office Action to generate said derivatives. Regarding the Examiner's specific comments about the variation of one or a few amino acids which may change the property of a protein, the disclosed specification has provided specific embodiments of Keyhole Limpet Hemocyanin being used as the immunogenic protein. The derivatives generated may easily be tested using the specific Keyhole Limpet Hemocyanin disclosed in the specification for comparison. Accordingly, there is no undue experimentation and applicants maintain that the derivatives of Keyhole Limpet Hemocyanin are fully enabled by the specification as filed.

In view of the foregoing discussion, applicants respectfully request the reconsideration and withdraw of the above ground of

rejection.

§103 Rejections

Claims 44-45, 47-48 and 53-56

The Examiner rejected claims 44, 45, 47-48 and 53-56 under 35 U.S.C. §103(a) as being unpatentable over Livingston, et al. (Cancer Research) in view of Ritter, et al., Livingston, et al. (U.S. Patent No. 5,102,663) and Ritter, et al. (1990) for the reasons set forth in the Office Action mailed 6/10/96.

The Examiner stated that in response to applicants' piecemeal analysis of the references, one cannot show non-obviousness by attacking references individually where, as here, the rejections are based on combinations of references.

The Examiner stated that applicants assert that the cited references do not suggest or motivate one of ordinary skill in the art to make the claimed invention. The Examiner stated that applicants' arguments are not persuasive for the reasons as set forth in the last Office Action.

The Examiner stated that applicants appear to argue that the rejection should be withdrawn since from the prior art (e.g. Ritter, et al.) does not suggest or provide an expectation that the oligosaccharide portion of ganglioside conjugate remains intact or needs to be intact. The Examiner stated that applicants' arguments are not persuasive to obviate the rejection since applicants' arguments are not commensurate in scope with the claimed invention. The Examiner stated that the claimed invention does not set forth that the oligosaccharide portion remains intact. The Examiner stated that beyond this while Rutter, et al. (1991) may not characterize that the oligosaccharide portion remains intact with conjugation as asserted by applicants, it would have been reasonable to expect the conjugate of the prior art would have the same properties of

the conjugate as claimed since conjugating the KLH to a ganglioside as set forth by Ritter, et al. and as recited enhances the antibody response.

The Examiner stated that applicants argue that the rejection should be withdrawn since the prior art does not teach of the requirement (e.g. need) for an adjuvant. The Examiner stated that applicants' argument is not persuasive since Livingston, et al. sets forth the vaccine administered to melanoma patient contains an adjuvant.

The Examiner stated that for the reasons set forth above and in the last Office Action, said rejection is maintained.

In response, applicants respectfully traverse the above ground of rejection. Applicants would like to point out the applicants have canceled claims 44-45, 47-48 and 53-56 without prejudice. New claims are directed to a composition comprising a ganglioside conjugated through the ceramide portion of the ganglioside to a Keyhole Limpet Hemocyanin or a derivative thereof and an adjuvant, the amounts of such conjugated ganglioside and such adjuvant being effective to stimulate or enhance antibody production in a subject, and a pharmaceutically acceptable carrier and uses of said composition.

Applicants maintain the cited references, alone or in combination thereof do not disclose, teaches or suggest the conjugation of a ganglioside through the ceramide portion of the ganglioside to a Keyhole Limpet Hemocyanin or a derivative thereof. The cited references, alone or in combination thereof, do not provide any SPECIFIC teaching that the conjugation should be carried at the Ceramide portion.

In addition, applicants further maintain that the cited references do not disclose, teaches or suggest the composition

comprising the a ganglioside conjugates and an adjuvant. Regarding the Examiner's comments about Livingston et al., applicants maintain that neither of the Livingston et al. disclose or teach the requirements of conjugation of the ganglioside to an appropriate carrier and an adjuvant. In fact, the combination of Livingston et al. teaches an ordinary skilled artisan away from the claimed invention because Livingston et aL (Patent) discloses the conjugated ganglioside is enough to produce an immune response and Livingston et al. (Cancer Research) uses a NON-CONJUGATED ganglioside with adjuvant. It is clear the combination of Livingston would suggest that it is not necessary to have both conjugation and adjuvant for a vaccine to be effective.

Accordingly, in view of the foregoing, applicants respectfully request the reconsideration and withdraw of the above ground of rejection.

Claim 49

The Examiner rejected claim 49 under 35 U.S.C. §103(a) as being unpatentable over Livingston, et al. (Cancer Research) in view of Ritter, et al., Livingston, et al. (U.S. Patent No. 5,102,663) and Ritter, et al. (1990) as applied to claims 44, 46-48, and 53-56 above and further in view of Kensil, et al. and Marciani, et al. for the reasons set forth in the Office Action mailed 6/10/96.

The Examiner stated that applicants appear to argue the rejection should be withdrawn since the prior art does not suggest or provide an expectation of making the claimed invention as applied to the claims above. The Examiner stated that for the reasons set forth above, applicants' arguments are not persuasive.

The Examiner stated that applicants assert that Kensil, et al. and Marciani, et al. do not suggest or motivate one of ordinary

skill in the art to make the claimed invention. The Examiner stated that applicants' arguments are not persuasive for the reasons as set forth in the last Office Action.

In response but without conceding the correctness of the Examiner's position and to expedite the prosecution of the subject application, applicants have canceled claims 49 without prejudice, thereby rendering this ground of rejection moot. Dependent claim 63 now recites the adjuvant which is a carbohydrate derviable from the bark of a Quillaja saponaria Molina tree, which is the subject matter of claim 49. As applicants have hereinabove discussed, there is no teaching for the requirement of a CONJUGATED GANGLIOSIDE and an ADJUVANT at the time of the applicants' invention. Applicants believe that the Examiner's comments have been addressed by the response to the above ground of rejection.

Claims 51 and 52

The Examiner rejected claims 51 and 52 under 35 U.S.C. §103(a) as being unpatentable over Livingston, et al. (Cancer Research) in view of Ritter, et al., Livingston, et al. (U.S. Patent No. 5,102,663) and Ritter, et al. (1990) as applied to claims 44, 46-48, and 53-56 above and further in view of Irie, et al. for the reasons set forth in the Office Action mailed 6/13/96.

The Examiner stated that applicants appear to argue the rejection should be withdrawn since the prior art does not suggest or provide an expectation of making the claimed invention as applied to claims above. The Examiner stated that for the reasons set forth above, applicants' arguments are not persuasive.

The Examiner stated that applicants' argument that the teaching that GM2 is found on melanomas and breast carcinomas by Irie, et al. does not provide sufficient motivation for one of ordinary skill in the art to practice the claimed invention is not

persuasive. The Examiner stated that since Livingston, et al. teaches of a vaccine for melanoma patients which stimulates the production of anti-GM2 antibodies and GM2 is associated with a variety of tumors (i.e. melanoma and breast) as taught by Irie, et al., one of ordinary skill in the art would have been motivated to use the vaccine composition not only melanomas as set forth by Livingston, but also breast carcinomas since both types of tumors have GM2 present. The Examiner stated that for the reasons set forth above and in the last Office Action, said rejection is maintained.

In response but without conceding the correctness of the Examiner's position and to expedite the prosecution of this subject application, applicants have hereinabove cancel claims 51 and 52 without prejudice. New claim 73 corresponds to the canceled claims 52 except that it ultimately depends on claim 57 which recites a composition comprising a ganglioside conjugated through the ceramide portion of the ganglioside to a Keyhole Limpet Hemocyanin or a derivative thereof and an adjuvant, the amounts of such conjugated ganglioside and such adjuvant being effective to stimulate or enhance antibody production in a subject, and a pharmaceutically acceptable carrier. Applicants have hereinabove discussed most of the references and would like to reiterate their position. The additional citation of Irie et al. in combination with the previous cited reference does not render the composition claim, claim 57 obvious and therefore cannot render the dependent claim 73 obvious. Accordingly, applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

In summary, for the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for objection and rejection set forth in the April 1, 1998 Office Action and earnestly solicit allowance of the claims now pending in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee, other than the FOUR HUNDRED AND SEVENTY-FIVE DOLLAR ($475.00) fee for a three-month extension of time is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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Albert Wai-Kit Chan 10/1/98
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